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MINIREVIEW

Potential Targets for Antifungal Drug Discovery Based on Growth and Virulence in *Candida albicans*

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Fungal infections, especially infections caused by *Candida albicans*, remain a challenging problem in clinical settings. Despite the development of more-effective antifungal drugs, their application is limited for various reasons. Thus, alternative treatments with drugs aimed at novel targets in *C. albicans* are needed. Knowledge of growth and virulence in fungal cells is essential not only to understand their pathogenic mechanisms but also to identify potential antifungal targets. This article reviews the current knowledge of the mechanisms of growth and virulence in *C. albicans* and examines potential targets for the development of new antifungal drugs.

In the last few decades, opportunistic fungal infections have been increasingly recognized as major causes of human diseases, especially among immunocompromised patients, such as transplant recipients, HIV/AIDS patients, and cancer patients (1). Systemic infection caused by *Candida* species is the fourth leading cause of nosocomial bloodstream infection in modern hospitals (2). The increasing rate of non-*Candida albicans* isolation and the rapidly growing resistance of *Candida* species present a challenging clinical problem (3). *C. albicans* is the most common etiological agent of candidiasis, causing not only superficial mucosal candidiasis but also life-threatening systemic infection in immunocompromised patients (3, 4). Only a few classes of antifungal agents, such as polyenes, azoles, allylamines, echinocandins, and miazines, are available, and their mechanisms are confined to targeting the cell envelope (wall and plasma membrane) and inhibiting DNA synthesis (5). In addition, most of these drugs exert serious unwanted effects on the host, such as nephrotoxicity caused by amphotericin B (6), visual disturbances caused by voriconazole (7), and congestive heart failure caused by itraconazole (8). In addition, some of these drugs, such as the echinocandins, are in limited clinical use due to high costs (9). Of particular importance today is the emergence of several *Candida* species resistant to many commonly used antifungal drugs, especially fluconazole (3, 10). Thus, there is an urgent and unmet need for the development of new antifungal drugs based on new antifungal targets.

Much work has been done to investigate the pathogenicity and resistance of various *Candida* species, most of it focused on *C. albicans*. Several physiological processes have been identified that contribute to the pathogenic potential of *C. albicans* (11). Rather than killing the fungal cells, which requires quite high specificity and may lead to the emergence of resistance, inhibiting growth and virulence factors in fungal cells represents a good alternative for the development of new antifungal drugs (12). Based on the considerations mentioned above, the purpose of this review is to summarize recent knowledge of the mechanisms of growth and virulence in *C. albicans* and to reveal potential drug targets. Numerous metabolic pathways, signal transduction pathways, invasion-related processes, and transcription factors are important for fungal pathogenicity, and only some processes which are studied widely and have great potential are included in this review. All of these processes and potential targets are depicted in Fig. 1.

Most of the targets described in this review lack human homologs and represent virulence factors instead of killing *Candida* cells. This review may help us to design highly specific antifungal drugs that avoid or minimize host side effects. If antifungal drugs designed on the basis of the potential targets described in this review can be successfully developed, they would be usable alone or in combination with current antifungal drugs (especially fluconazole) to treat *Candida* infections.

POTENTIAL DRUG TARGETS IN *C. ALBICANS*

Glyoxylate cycle. The metabolic pathways in *C. albicans* are essential for its virulence. The glyoxylate cycle is a modified tricarboxylic acid (TCA) cycle that bypasses the CO_2-generating steps to conserve carbons as substrates for gluconeogenesis. This metabolic pathway enables *C. albicans* to survive in nutrient-limited host niches and is a prerequisite for the virulence of *C. albicans* (13, 14). It consists of five enzymes, including isocitrate lyase (ICL) and malate synthase (MLS), which are unique to this cycle, and three others that are shared with the TCA cycle (15). ICL, as one of the unique enzymes involved in the glyoxylate cycle, is essential for the virulence of *C. albicans* as well as several other pathogens, such as *Aspergillus fumigatus* (16), *Magnaporthe grisea* (17), *Burkholderia pseudomallei* (18), and *Mycobacterium tuberculosis* (19). *C. albicans* mutants lacking ICL fail to utilize acetate, ethanol, citrate, glycerol, lactate, and pyruvate (15, 20, 21).Additionally, these mutants are less persistent in internal organs and

Accepted manuscript posted online 20 July 2015

Citation Li X, Hou Y, Yue L, Liu S, Du J, Sun S. 2015. Potential targets for antifungal drug discovery based on growth and virulence in *Candida albicans*. Antimicrob Agents Chemother 59:5885–5891. doi:10.1128/AAC.00726-15.

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doi:10.1128/AAC.00726-15

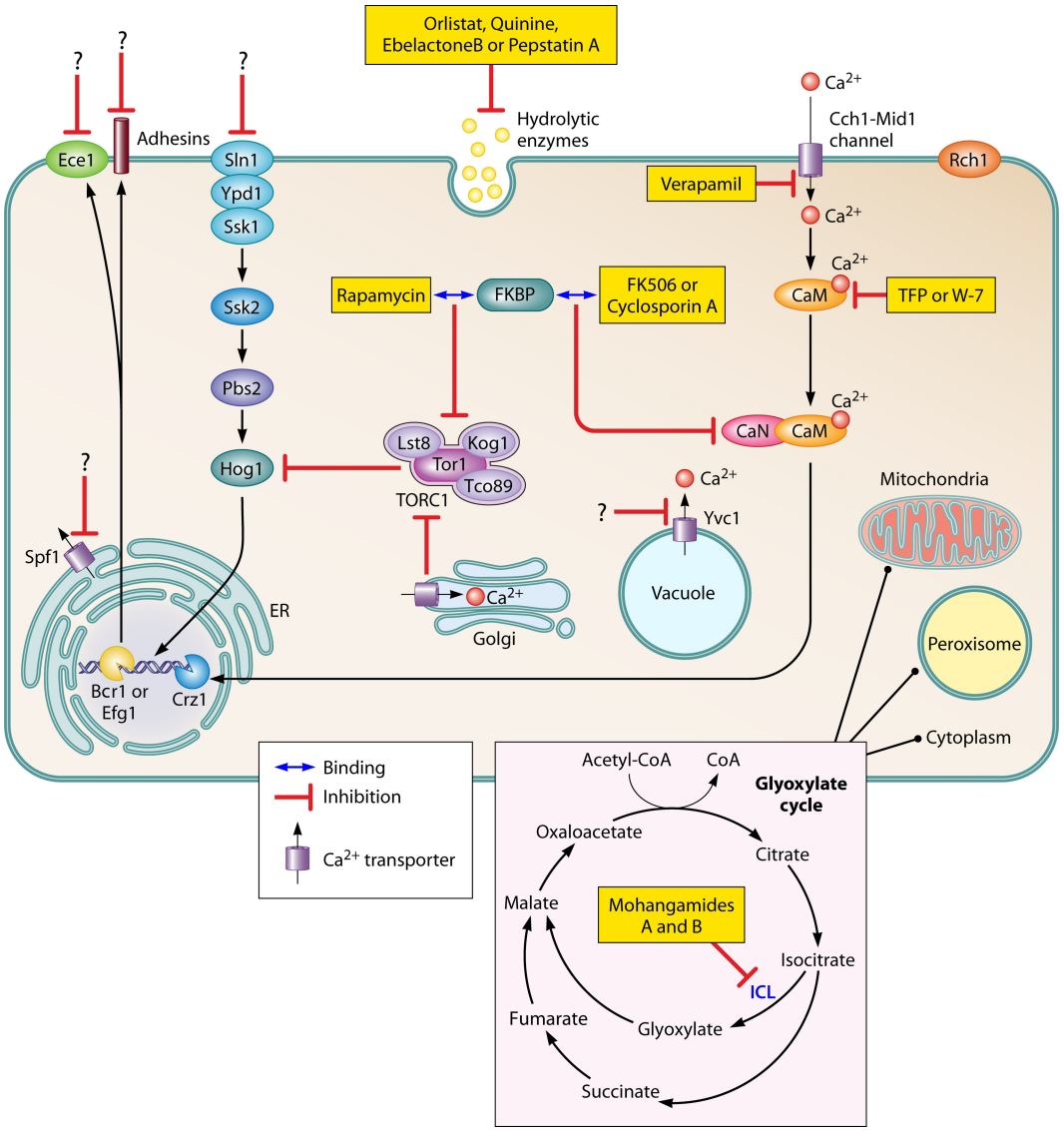

FIG 1 A schematic diagram depicting the potential antifungal targets for antifungal drug development in *C. albicans*. Inhibitors of some potential targets that have not been found to date are shown by the use of a question mark ("?"). CoA, coenzyme A; ER, endoplasmic reticulum.

are markedly less virulent in mice than the wild type (22). In addition, the glyoxylate cycle does not exist in the mammalian host, making it or its unique enzymes valuable targets for the development of antimicrobial drugs (13, 14). Therefore, ICL is a promising target for antimicrobial drug discovery, and specific ICL inhibitors might be less toxic to the host than antifungal drugs that inhibit many conserved processes.

Several inhibitors of ICL, including 3-nitropropionate, 3-bromopyruvate, 3-phosphoglycerate, mycenon, oxalate, and itaconate, have been identified (23). However, most of these inhibitors are not pharmacologically suitable for use *in vivo* due to their toxicity and nonspecificity. Thus, natural specific inhibitors of ICL derived from organisms have been sought as they may have many suitable pharmacological properties (24). In recent years, two compounds, mohangamide A and mohangamide B (25), isolated from a marine actinomycete *Streptomyces* sp., have shown specific inhibitory activity against the ICL of *C. albicans*, which paves the way for new ICL inhibitor design.

Further development of selective ICL inhibitors with suitable pharmacological properties would require more tests in animal models to establish both the importance of the glyoxylate cycle in *C. albicans* and the evidence for the therapeutic potential of ICL inhibitors in fungal infections. Although several compounds have inhibitory activity against ICL in *C. albicans*, there is still much to be learned before these compounds can be considered viable drug candidates for treatment of *C. albicans* infections. We hope that new structural ICL inhibitors developed by modification of existing ICL inhibitors will soon be identified.

HOG pathway. For pathogens, it is especially important to respond to the different microenvironments presented by the host. The mitogen-activated protein kinase (MAPK) pathway is one of the most important eukaryotic signal networks allowing adaptation to environmental changes (26). Four MAPK signaling pathways in *C. albicans* have been identified: the Mkc1 pathway, the Cek1 pathway, the Cek2 pathway, and the high-osmolarity glycerol (HOG) pathway (27). By genetic analysis and phenotypic

characterization of mutants, these pathways in *C. albicans* have been extensively characterized as involved in invasive hyphal growth, morphogenesis, biogenesis of the cell wall, dimorphism, and the stress response, all of which have long been speculated to play an important role in *C. albicans* pathogenicity or in its virulence (26, 28–34). The accumulation of these findings supports the idea that functional MAPK signaling pathways are essential for the maintenance of full virulence of *C. albicans*. Thus, the components of these pathways may be suitable as targets for developing new fungicides.

Among the four MAPK signaling pathways in *C. albicans*, the HOG pathway is of great interest. It is composed of a two-component-system (TCS)-like phosphorelay system and the Hog1-type mitogen-activated protein kinase cascade. The former consists of Sln1, Ypd1, and Ssk1, and the latter consists of Hog1, Pbs2, and Ssk2. The TCS is conserved in a wide range of organisms from bacteria to higher plants but not in mammals (35), which suggests that the TCS is a promising molecular target for new antifungal drugs with lower toxicity to the host. Hog1 can be repressed by reducing Tor1 activity levels by rapamycin administration (36). Two compounds, 4- and 5-substituted 1,2,3-triazoles, potentially and selectively inhibit Hog1 in *Saccharomyces cerevisiae* (37). Therefore, disturbing the HOG pathway by modulating the unique TCS or by structural modification on the basis of existing Hog1 inhibitors may provide an unprecedented opportunity to develop novel antifungal drugs without severe side effects for the host.

TOR signaling pathway. Target of rapamycin (TOR) is a member of the phosphoinositide 3-kinase-related protein kinase family that is important for normal physiology in eukaryotes (38). It was originally identified in the budding yeast *S. cerevisiae* (39). Two functionally distinct TOR complexes, TOR complex 1 (TORC1) and TOR complex 2 (TORC2), have been described in various eukaryotes, such as *S. cerevisiae*, *S. pombe*, and mammals (39–41). TORC1 contains Tor1 or Tor2, Kog1 (encoded by *YHR186c*), and Lst8. TORC2 contains Tor2, Avo1 (encoded by *YOL078w*), Avo2 (encoded by *YMR068w*), Avo3 (encoded by *YER093c*), Lst8, and Bit61. Rapamycin is a microbial product with immunosuppressive properties that results primarily from a selective inhibition of T lymphocyte activation and is widely used during solid-organ transplantation (42, 43). It was first found to inhibit *C. albicans* and was later determined to have antifungal activity against *Cryptococcus neoformans* (44). TORC1 is potently and specifically inhibited by rapamycin, whereas TORC2 is not directly sensitive to rapamycin. The cytoplasmic protein FK506-binding protein (FKBP) is the direct receptor of rapamycin, and then the rapamycin-FKBP complex inhibits TORC1 activity (45).

Although rapamycin is currently used clinically as an immunosuppressive agent, its antifungal property triggered interest in the TOR signaling pathway. In recent years, studies have shown that the TOR signaling pathway plays a crucial role in various growth-related processes of yeast and higher eukaryotes (45–47). Most work has focused on the role of the TOR signaling pathway in multicellular organisms. Only a few studies show the contribution of this pathway in regulating virulence in *C. albicans* (48, 49). Morphogenesis in *C. albicans* is crucial for its virulence (50). The fact that *C. albicans* mutants lacking Mds3 or Sit4, each a member of the TOR signaling pathway, show defects in morphogenesis demonstrates an important role of the TOR signaling pathway in *C. albicans* virulence (48). Although how Mds3, Sit4, and Tor1 interact with each other is not yet understood, it is hypothesized that Sit4 is *C. albicans* specific, making it an ideal target for the treatment of *C. albicans* infections. In addition, as a member of the TORC1 complex in a few fungal species, the Tco89 sequence homolog does not exist in the mammals whose genomic sequences are available to the public, which also makes Tco89 a perfect antifungal target (51, 52).

Further understanding of the exact role of Mds3, Sit4, and Tco89 in the TOR signaling pathway should help us to develop specific drugs to treat *C. albicans* infections. Moreover, structural modification studies of rapamycin may also help us to identify more compounds with anti-*Candida* activity.

Cell calcium homeostasis. The maintenance of cell calcium homeostasis is required for the survival and pathogenicity of fungi. Studies of calcium homeostasis systems and calcium signaling pathways indicate that they are closely associated with numerous physiological processes in *C. albicans*, such as stress responses, virulence, hyphal development, and adhesion (53–56). Illuminating calcium-related mechanisms of pathogenicity in *C. albicans* may assist in establishing new control measures for its infection.

As one of the calcium signaling pathways in *C. albicans*, the calcium cell survival (CCS) pathway mediates cell survival in response to various environmental stresses. It triggers Ca^{2+} influx through the Cch1-Mid1 channel and activates calcineurin and its downstream transcription factor Crz1p (53). The Cch1-Mid1 channel is strongly associated with calcium homeostasis and is found in fungal cell membranes. The transcription factor Crz1p is a calcineurin target discovered in *C. albicans* (57). Calmodulin is a small, ubiquitous Ca^{2+}-binding protein which is found in all eukaryotic organisms and is highly conserved. Calmodulin plays a role in mediating CCS and the response to other stressors in *C. albicans*. The Cch1-Mid1 channel, calcineurin, Crz1p, calmodulin, and other components connected with calcium homeostasis systems could be potential drug targets in *C. albicans* (57). Deletion of *CCH1* or *MID1* in *C. albicans* was associated with depressed virulence in a mouse model and depressed the oxidative stress response phenotype (53, 58). Several studies have demonstrated that the antifungal activity of fluconazole is enhanced by combination treatment with FK506 or cyclosporine, both of which are calcineurin inhibitors and are currently used as immunosuppressants in clinical settings (59, 60). In addition, Sato et al. (2004) confirmed that the calmodulin-specific inhibitors TFP and W-7 suppress hyphal growth in *C. albicans* by preventing the expression of hypha-specific mRNAs (61). Moreover, verapamil, a calcium channel blocker, has inhibitory effects on hyphal development, adherence, gastrointestinal colonization, and biofilm formation in *C. albicans* (54, 55, 62).

In addition to CCS, there are other novel components in the calcium homeostasis systems of *C. albicans* that have the potential to be new drug targets. Yu et al. (2013) recently identified a putative endoplasmic reticulum (ER) Ca^{2+} pump in *C. albicans*, called Spf1, which is essential for many physiological processes in this pathogen (63). A Spf1 null mutant exhibited severe defects in growth rate, hyphal development, biofilm formation, and maintenance of cellular calcium homeostasis and was significantly attenuated in virulence (56). These findings provide phenotypic evidence for the importance of Spf1 in *C. albicans*. Recently, a putative vacuolar calcium channel, Yvc1, which localizes on the vacuolar membrane and plays a role in the stress response path-

way, was also identified in *C. albicans* (64). In one study, disruption of its encoding gene, *YVC1*, led to defects in the response to environmental stresses and in morphogenesis and resulted in attenuated virulence in a mouse model and in human epithelial cells (65). The lack of a vacuole in human cells makes Yvc1 an ideal target for the development of antifungal drugs. *C. albicans* plasma membrane protein Rch1 is also thought to be a novel regulator of cytoplasmic Ca^{2+} homoeostasis. *C. albicans* strains lacking *RCH1* are characterized by higher Ca^{2+} influx, an elevated cytoplasmic Ca^{2+} level, and activation of Ca^{2+}/calcineurin signaling (66).

It is clear that maintenance of cell calcium homeostasis is crucial for the pathogenicity of *C. albicans*. Further detailed molecular exploration of the calcium signaling pathways is required to decipher more fungus-specific components with lower host immunosuppressive cross-reactivity. We believe that the relationship between cell calcium homeostasis and *C. albicans* pathogenicity will be fully understood with ongoing research in calcium signaling pathways. Future research on calcium homeostasis systems or calcium signaling pathways of *C. albicans* and other pathogenic fungi may provide a theoretical basis for the development of new antifungal drugs.

Invasion-related hydrolytic enzymes. Secreted hydrolytic enzymes enable fungi to breach and invade host tissues (67).Recently, secreted hydrolytic enzymes have attracted much attention as potential virulence factors in fungi. The most highly recognized extracellular hydrolytic enzymes are proteinases, lipolytic enzymes, lipases, and phospholipases.

A number of studies have suggested that the absence or decreased expression of these hydrolytic enzymes may lead to reduced virulence of *Candida* species, and these enzymes have been shown to contribute to *C. albicans* morphological transition, colonization, cytotoxicity, and penetration of the host (67, 68). Evidence from one study strongly suggested that the invasive *C. albicans* strains exhibited significantly stronger extracellular phospholipase activity than the noninvasive strains (69). Mattei et al. (2013) reported that high levels of phospholipase and germ tube production in *C. albicans* can facilitate permeability of the epithelial barrier because phospholipase activity is concentrated in hyphal tips (70).In addition, the secreted aspartyl proteinases (Saps) of *C. albicans* are important virulence factors which make this pathogen more adapted than others to overcoming residual host barriers to infection (71, 72).

Orlistat is an irreversible inhibitor of human pancreatic lipase. The results of a docking study have shown 10 binding possibilities for orlistat in the active site of *Candida rugosa* lipase, showing the potential of orlistat as a new candidate for candidiasis treatment (73). Quinine, a lipase inhibitor, could slow the growth of *Candida* species (74). Moreover, the lipase inhibitor ebelactone B and the proteinase inhibitor pepstatin A were also reported to reduce the damage to human tissues caused by *Candida* species (74, 75). A greater effort in understanding the roles of the hydrolytic enzymes in fungal pathogens is needed, although it is clear that hydrolytic enzymes play an important role in the pathogenicity of several *Candida* species (67, 68).

The relationship between fungal hydrolytic enzymes and the diverse mechanisms of pathogenicity not only makes these hydrolytic enzymes potential targets for antifungal therapeutic intervention but also provides a theoretical basis for the development of fungal hydrolytic enzyme inhibitors, especially because fungal hydrolytic enzymes are not likely to be similar to their human homologs.

Biofilm-related transcription factors. The fungal pathogen *C. albicans* is frequently associated with catheter-based infections because of its ability to form biofilms. The medical consequences of catheter-based infections, such as potentially life-threatening systemic infections and device malfunctions, can be disastrous. The management of this type of infection is difficult and costly (76). Hence, searching for novel targets related to biofilm formation in *C. albicans* and developing the corresponding specific drugs are very important.

Hyphae are among the prominent features of *C. albicans* biofilms and may provide an adherent scaffold that stabilizes the biofilm structure (77). Six transcriptional regulators form a tightly woven network controlling biofilm development in *C. albicans* (78). Among them, Efg1 and Bcr1 are the most studied. *BCR1* is a downstream gene of the hyphal regulatory network that couples the expression of cell surface genes to hyphal differentiation, and zinc finger transcription factor Bcr1, encoded by *BCR1*, is one of the central regulators of biofilm formation (79, 80). Bcr1 is thought to be a positive regulator of adherence, and *bcr1/bcr1* insertion and deletion mutants form only rudimentary biofilms on silicone catheter material *in vitro* (80, 81). Efg1 is one of the best-characterized regulators of morphogenesis and metabolism in *C. albicans* (82). Efg1 is also required for numerous processes beyond the regulation of morphogenesis, such as biofilm formation (83) and virulence (84). Many target genes controlled by Bcr1 and Efg1 were identified initially as hypha-specific genes, such as *ALS1*, *ALS3*, and *HWP1* (81, 85). The adhesins Als1, Als3, and Hwp1 all contribute to biofilm formation (81, 86). Thus, Bcr1 and Efg1 as well as genes under their control may be new drug targets that permit more therapeutic strategies for catheter-based infections.

Also worth mentioning is the *ECE1* gene, which is a hypha-induced gene. It is also one of the Bcr1-dependent genes in *C. albicans* (87). Some research suggests that Ece1 plays a role in adhesion, which provides the first functional insight into this protein (81). The idea that Ece1 functions in adhesion is also supported by the observation that its overexpression restored the biofilm formation of a *bcr1/bcr1* mutant (81). Its role in adhesion makes it an ideal target for our purpose, although its detailed mechanism of action is unclear.

No compound with the ability to inhibit these factors has been identified. New drugs based on the potential targets mentioned above may be useful for the treatment of catheter-based infections because adhesion and biofilms contribute to the pathogenicity of *C. albicans*.

Other physiological processes with potential antifungal targets. There are other possible pathogenic processes and potential targets in *C. albicans* that have not been investigated in detail, such as the metabolic pathway of arachidonic acid and reactive oxygen species (ROS) homeostasis, that are intriguing.

Prostaglandin production from arachidonic acid is critical for growth in *C. albicans* and could be a significant virulence factor in biofilm-associated infections, revealing great implications for understanding the mechanisms of *Candida* infections (88, 89). The ability to adapt to oxidative stress also plays an important role in the pathogenicity of *C. albicans* because oxidative killing is a major mechanism to counteract pathogens (90). The exact role of ROS in fungal pathogenicity and biofilm development is complex and

remains unclear. However, compounds disturbing ROS homeostasis, such as shikonin, show powerful action against *C. albicans*, which suggests the important role of ROS homeostasis in the pathogenicity of *C. albicans* (91).

Future studies of the exact targets connected with the processes mentioned above are important for understanding the fundamental mechanisms of *C. albicans* and the development of new antifungal drugs.

DISCUSSION AND FUTURE PERSPECTIVES

The *C. albicans* metabolic pathways, signal transduction pathways, invasion-related processes, and transcription factors described above have been studied widely and are essential not only for growth of fungi but also for their virulence. Reducing the virulence of fungi by targeting their pathogenic processes, rather than trying to eradicate them completely from the microbiota, which often turns out to be very difficult, represents a very attractive approach for the development of new antifungal drugs.

Many existing antifungal drugs exert serious unwanted effects on the host, which is of clinical importance. In recent years, advances in the search for new targets for anti-*Candida* drugs have been achieved, as reflected by the abundant literature disclosing therapeutic strategies. Most of the potential targets described in this review have no homolog in human cells or are highly specific for *C. albicans*, which means that antifungal drugs based on these targets may be highly specific and less toxic. It is worth mentioning that some processes in this review are interactive. For example, Pmr1, a Golgi complex-localized ATPase that transports Ca^{2+} from the cytoplasm into the Golgi complex, functions as a negative regulator of the rapamycin-sensitive TORC1 protein (92, 93). FKBP plays roles both in the TOR signaling pathway and in the calcium signaling pathways (45, 94). Reduced Tor1 activity caused by rapamycin suppresses the basal activity of Hog1 in the HOG pathway (36). The interactions among these processes also indicate the enormous potential of the targets described above to be good antifungal targets. Designing new inhibitors of these novel targets or modifying the structure on the base of existing inhibitors might lead to a deeper understanding of the pathogenic mechanisms of *C. albicans* in addition to more treatment options for *C. albicans* infections.

Although compound discovery is much more difficult in comparison to the discovery of fungus-specific targets, there is an inspirational example for compound discovery (37). Although there is no exact structural information available for Hog1 in yeast, Hog1 is very similar to mammalian MAPK p38, a homolog of yeast Hog1, with 51% identity at the amino acid level. Dinér et al. (37) built homology models of Hog1 based on structural information from p38, and one of them showed high conservation of the amino acid residues in the ATP-binding cleft between Hog1 and p38, suggesting that the binding motif of inhibitors in p38a could potentially be used to guide the development of Hog1 inhibitors. A new series of 4- and 5-substituted 1,2,3-triazoles were then designed to have amine functionality in position 2 of the pyridine ring that could potentially form an extra hydrogen bond with the hinge region. Additionally, they found that the binding mode of the amine-containing triazoles is similar to the binding mode of a known p38 inhibitor. On this basis, two Hog1 inhibitors were successfully synthesized.

The generation of new antifungal drugs against *C. albicans* should be a joint effort by pharmacologists, pathologists, chemists, and medical scientists. Further investigations *in vitro* and *in vivo* are required to demonstrate the effectiveness of the potential inhibitors, and all of them should be carefully evaluated in a comprehensive manner with special reference to toxicity, efficacy, long-term survival, quality of life issues, and health economics parameters. We have every reason to believe that the generation of new antifungal drugs will be achieved in the near future with continued progress in the molecular understanding of fungal pathogenic mechanisms.

ACKNOWLEDGMENTS

This work was supported by grants 2013GSF11848 from the Department of Science and Technology of Shandong Province of China, ZR2011HL049 from Shandong Provincial Natural Science Foundation of China, and 2013-196 from Shandong Provincial Administration of Traditional Chinese Medicine of China.

We declare that we have no conflicts of interest.

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